REMARKS

Claims 9, 11-17, and 21-97 are pending in the case, new claims 59-97 having been added by the above amendment. Support for the new claims can be found throughout the application, e.g., at page 5, lines 2-4 and 14-29, and page 6, lines 1-15. No new matter has been added. Applicants ask that the new claims be considered with the previously presented claims.

The Office action dated March 5, 2010 (the "Office action") rejects all of the pending claims under 35 USC § 103(a) as unpatentable over Smeenk et al., "Opportunistic Lung Infections in Patients with Chronic Obstructive Pulmonary Diseases – A Side Effect of Inhalation Corticosteroids?", *Nederlands Tijdschrift voor Geneeskunde*, Vol. 13, Issue 140, pages 94-98, 1996 (the English translation of which is hereinafter referred to as "Smeenk"), in view of Carling (WO 93/11773; "Carling"). Applicants traverse on a number of grounds, as detailed below.

Smeenk summarizes case histories of four patients in the Netherlands whose Chronic Obstructive Pulmonary Disease (COPD) was treated with inhaled budesonide and other drugs, and each of whom contracted an opportunistic lung infection. See pages 2-3 of Smeenk. The Office action at page 3 characterizes Smeenk's teachings regarding one of these four patients, Patient B, as follows:

> Smeenk et al teach that a 66-year-old man, was being treated for a moderately severe COPD with formoterol 12ug 2 times a day and budesonide 800ug 2 times a day via an inhaler (Turbuhaler).

The pertinent passage of Smeenk actually reads in full:

> Patient B, a 66-year-old man, was seen by us at the end of 1994 due to a new peripheral anomaly in the superior lobe of the left lung (Figure 2). Since 1991, he was being treated for a moderately severe COPD with theophylline 300 mg in retard form 2 times daily, ipratropium 80 μg 4 times daily, formoterol 12 μg 2 times daily, and budesonide 800 μg 2 times daily via an inhaler (Turbuhaler).

In the quoted passage, Smeenk names the various drugs that were tried by Patient B at some point over the course of the period from 1991 to the end of 1994. Smeenk does not say that the patient was treated with all four of the named drugs from the beginning to the end of the entire period from 1991 to 1994, and does not imply that any two or more were administered on the

same day at any point during that period. The four drugs could very well have been tested in series, one at a time, with no overlap, in an attempt to find a drug that helped the patient's symptoms while minimizing side effects. (In fact, testing two or more simultaneously would make it difficult to determine whether any observed improvement or side effects were due to just one of the drugs, and if so, which one, or due instead to the combination.) There is simply too little detail in this reference to permit one to conclude one way or the other about which (if any) of the four drugs might have been used at the same point in time as another of the four. There is certainly no indication that the patient was treated simultaneously with formoterol in particular and budesonide in particular at any point in time. All one can conclude about timing of treatment is that, during the 1991-1994 time period, the patient was treated with theophylline at some point, and with ipratropium at some point, and with formoterol at some point, and with budesonide at some point, and that the treatment with budesonide was apparently continuing when Smeenk first saw the patient in 1994 (because Smeenk says the inhaled corticosteroid treatment was "terminated" when the infection was diagnosed).

In fact, it is highly unlikely that Smeenk was saying that the patient was treated with all four drugs simultaneously throughout the period from 1991 to 1994. Applicants base this conclusion on the fact that one of the four drugs, formoterol, was not even approved for marketing in the Netherlands until 1992. Reference 18 cited in the Information Disclosure Statement submitted on even date herewith is a one-page Product Information sheet from the Medicines Data Bank followed by a nine-page printout from the register of the Medicines Evaluation Board of the Netherlands, both indicating that Foradil® (formoterol) received marketing authorization RVG 14320 in the Netherlands on 4 March 1992 (see the Product Information sheet and also the last page of the nine-page printout). One of ordinary skill in the art would understand from Smeenk that Patient B received formoterol at some point during the period from 1991 to 1994, but would understand it was not during the whole period (since it was not even marketed in the Netherlands for the whole period), and possibly only for a short time. The person of ordinary skill in the art would realize that no further conclusions could be drawn

about when during the 1991-1994 time frame each of the four drugs was taken, nor for how long, nor in what (if any) combinations. Smeenk simply does not say.

Second, Smeenk does not report whether any of the four listed drugs was actually efficacious in treating Patient B's COPD. In fact, the only evidence bearing on efficacy of any of the drugs used by any of the patients concerns the ICS (inhaled corticosteroid; i.e., budesonide)[1] that was being used by each of the patients at the time of the study, and implies that, if anything, budesonide was not of observable benefit to the patients. See page 10, where Smeenk refers to the table on page 11 and notes that "**[a]fter the administration of ICS to our patients was terminated, the exhalation disorder of our patients turned out not to deteriorate any further**." Since the patients' COPD disorder did not worsen after termination of budesonide treatment, this suggests that budesonide treatment was not helping alleviate the disorder. The lack of observed beneficial effect of budesonide on the COPD disorder is consistent with Smeenk's comments on page 2 that "[t]he efficacy of ICS in the treatment of patients with a chronic obstructive pulmonary disease (COPD), however, is still very controversial." Smeenk teaches that, as of 1996, there was no solid evidence that inhaled corticosteroids are at all useful in treating COPD. Smeenk's own evidence indicates that budesonide treatment was of no apparent benefit in his COPD patients.

Third, it is important to note that the real point of the article is not about efficacy of drugs used to treat COPD, but rather about a possible side effect of inhaled corticosteroids in COPD: increased susceptibility to opportunistic lung infections. See, e.g., the title of the article. After presenting case histories of four COPD patients who had been receiving treatment with inhaled budesonide and who were subsequently diagnosed with "opportunistic" mold or mycobacterial lung infections, Smeenk discusses at page 9 the biological effects of steroids in suppressing the function of immune cells, including the cytotoxic T cells that are important in combating mold and mycobacterial infections in particular. Smeenk says at page 10:

> It appears plausible to us that there is a causal relationship between the long-term use of a relatively high dose of ICS that was administered to our 4 patients and the occurrence of mycobacterial and mold infections in the lungs of our patients. The relationship between

[1] The inhaled corticosteroid used by each of the four patients was budesonide.

> such opportunistic infections and the use of oral corticosteroids has been repeatedly described in the literature....On the basis of our own observations and those of Shaikh, we believe that caution should be exercised in the long-term prescription of ICS to patients with a COPD, because there is a possibility of a risk of the occurrence of opportunistic infections, and because the clinical effectiveness of these medications for these disorders has not been established in any way.

By drawing this link between inhaled corticosteroids and opportunistic lung infections (which are potentially very serious in COPD patients), and by demonstrating that the four patients' COPD symptoms were no better during treatment with budesonide than after the budesonide treatment was terminated, Smeenk provides powerful evidence that inhaled corticosteroids in general (and budesonide in particular) are unlikely to be useful in treating COPD, and may carry a significant risk. Thus, Smeenk emphatically *teaches away* from use of budesonide to treat COPD, whether alone or in combination with another drug such as formoterol.

The second reference cited in this obviousness rejection is Carling. Carling has been extensively discussed (and repeatedly overcome) as the primary reference in a series of obviousness rejections during the course of this lengthy prosecution. According to the Office action at page 3, Carling is presently cited for its teaching "that the formoterol and budesonide are available in a single medicament for simultaneous administration by inhalation," and for an alleged disclosure of certain advantages of the combination. Carling's teachings relate to treatment of asthma, not COPD, and indeed the Office action does not rely on Carling as teaching anything about COPD. Rather, the rejection is premised on the alleged obviousness of using Carling's formoterol/budesonide combination to treat Smeenk's Patient B, who was described as having been treated with, among other drugs, formoterol and budesonide (though not necessarily simultaneously, as discussed above). According to the Office action at page 4,

> It would have been obvious to one of ordinary skill in the art to employ the Carling's medicament in the treatment of COPD in the COPD patient disclosed by Smeenk et al. One would have been motivated to make such a modification in order to achieve [an] expected benefit of the Carling et al's medicament comprising both formoterol and budesonide...

Applicants submit that it would not have been at all obvious to treat any of Smeenk's patients with Carling's formoterol/budesonide combination, for at least the simple reason that budesonide

had been tried in each of the four patients and was considered by Smeenk to have been responsible for the opportunistic lung infection each patient contracted during treatment. Furthermore, Smeenk reported that the patients' COPD symptoms did not worsen after budesonide treatment was terminated, suggesting that budesonide treatment had proven to be worthless in these patients. In view of Smeenk's teachings, it therefore cannot be said to have been "obvious" to begin treating Patient B or any of the other patients again with a budesonide-containing medicament such as Carling's. Quite the opposite: one of ordinary skill would know to avoid ever trying budesonide in these patients again.

Applicants remind the Examiner of other evidence already of record regarding teachings-away in the prior art. Watson *et al.,* Chest 101:350-355, 1992 (reference B7 in the Information Disclosure Statement filed December 8, 2008), and Wempe *et al.*, Thorax 47:616-621, 1992 (reference B8 in the same Information Disclosure Statement), were discussed by Applicants on pages 4-5 of the Reply filed December 8, 2008. Watson *et al.* showed that, consistent with previous studies with budesonide in COPD, a relatively high dose of inhaled budesonide (1200 μg per day) did not improve lung function in smokers with mild airflow obstruction, and did not improve response to either of two bronchodilators (salbutamol and ipratropium bromide). See the abstract at page 350. Likewise, Wempe *et al.* found that even higher doses (1600 μg per day) of inhaled budesonide had no significant effect on lung function in COPD patients (page 619, first column), and did not improve the patients' response to the same two bronchodilators—salbutamol and ipratropium bromide (page 619, first column, and page 620, Figure 3). Although not prior art, a third publication, Vestbo et al., Lancet 353:1819-1823, 1999; submitted with the Information Disclosure Statement filed November 4, 2005, shows that even after Applicants' priority date, those of skill in the art were still saying that "**Inhaled budesonide was of no clinical benefit in COPD patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD.**" *See*, abstract. The Examiner referred in particular to the teaching-away in Watson *et al.* when explaining her Reasons for Allowance in the Notice of Allowability dated March 13, 2009.

Nothing in Smeenk nor Carling contradicts those teachings-away; indeed, as described at length above, Smeenk also firmly teaches away from using budesonide to treat COPD. As emphasized by the U.S. Supreme Court in *KSR v. Teleflex,* 127 S.Ct. 1727 (2007), a teaching-away in the art has long been considered highly relevant evidence of nonobviousness.

Applicants submit that, in view of the evidence of record, one of ordinary skill in the art would have perceived no reason to try using Carling's formoterol/budesonide medicament in treating Smeenk's COPD patients (or any COPD patients, for that matter) at the priority date. There certainly would have been no expectation of success. Accordingly, a proper *prima facie* case of obviousness has not been made out.

Further, Applicants remind the Examiner of the extensive objective evidence of nonobviousness already of record in this application. This includes evidence of both surprising results and skepticism of experts, all of which must be taken into account when considering whether the claimed methods are obvious.

Surprising results

The Reasons for Allowance set forth in the Notice of Allowability dated March 13, 2009, point to the surprising results in the Declaration of Jan Trofast originally submitted by Applicants on November 4, 2005 (the "2005 Declaration"), as supporting the nonobviousness of the claims. The data in the 2005 Declaration and a related publication (Calverley *et al.*, Eur. Resp. J. 22:912-929, 2003) were discussed in detail by Applicants at least three times during this prosecution: in the Reply filed November 4, 2005; in the Brief on Appeal filed March 7, 2007, and in the Reply filed December 8, 2008. Rather than repeat those remarks yet again, Applicants urge the Examiner to review what is already of record. For example, see pages 13-18 of the Brief on Appeal filed March 7, 2007, for a point-by-point analysis of the data. These data reveal that the combination of budesonide and formoterol produces dramatic and surprising synergistic results in the treatment of COPD, by each of several different measures of efficacy (any one of which would be sufficient to overcome a *prima facie* obviousness case, had one been made out). That the results are indeed surprising was acknowledged by the Examiner in the aforementioned

Notice of Allowability. Applicants submit that the newly cited Smeenk reference does nothing to neutralize the unexpectedness of these clinical results—in fact, if anything, the teaching-away in Smeenk makes the positive benefits reported in the 2005 Declaration and in Calverley *et al.* all the more unexpected.

Additional post-filing date evidence of successful use of the budesonide/formoterol combination in treating COPD is found in the following publications:

Szafranski et al., "Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease," Eur Respir J 21:74-81 (2003) (cited in the Information Disclosure Statement filed November 4, 2005)

Rennard et al., "Efficacy and Tolerability of Budesonide/Formoterol in One Hydrofluoroalkane Pressurized Metered-Dose Inhaler in Patients with Chronic Obstructive Pulmonary Disease," Drugs 69(5): 549-565 (2009) (cited in the Information Disclosure Statement filed on even date herewith)

Tashkin et al., "Efficacy and Safety of Budesonide and Formoterol in One Pressurized Metered-Dose Inhaler in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease," Drugs 68(14): 1975-2000 (2008) (cited in the Information Disclosure Statement filed on even date herewith)

Welte et al., "Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease," Am J Respir Crit Care Med 180: 741-750 (2009) (cited in the Information Disclosure Statement filed on even date herewith)

Calverley et al., "Preventing mortality in COPD; the value of inhaled budesonide added to bronchodilators," Abstract #34 presented at COPD5, 5th International Multidisciplinary Conference on Chronic Obstructive Pulmonary Disease, 28-30 June 2006, Birmingham, UK (cited in the Information Disclosure Statement filed on even date herewith)

Partridge et al., "Effect on lung function and morning activities of budesonide/formoterol versus salmeterol/fluticasone in patients with COPD," Therapeutic Advances in Respiratory Disease 3(4): 147-157 (2009) (cited in the Information Disclosure Statement filed on even date herewith)

None of the results reported in the above post-filing date publications could have been predicted in view of Smeenk, Carling, or any other art of record, particularly given the teachings-away in the art. Accordingly, these results further support the nonobviousness of the claimed methods.

Skepticism of Experts

Two post-filing date publications, both already of record, illustrate that the skepticism in the art about the potential usefulness of budesonide or a formoterol/budesonide combination for treating COPD persisted even after the present application's 1997 priority date. The first of these post-1997 publications is the Vestbo et al. 1999 article mentioned above. As noted above, Vestbo et al. was quite dismissive about the use of budesonide in COPD: "**Inhaled budesonide was of no clinical benefit in COPD patients recruited from the general population by screening. We question the role of long-term inhaled corticosteroids in the treatment of mild to moderate COPD.**" Years later, even after publication of two clinical trials disclosing the benefits of formoterol/budesonide combination therapy in COPD, an editorial by K.F. Rabe expresses one expert's lingering disbelief in the potential usefulness of such therapy. See Rabe, Eur Respir J 22:874-875 (2003), cited in the Information Disclosure Statement filed March 1, 2004. Dr. Rabe acknowledged that, while he was "happy to adopt" use of a formoterol/ budesonide combination therapy for treatment of asthma, **he was skeptical that the combination could be generally useful in treatment of COPD**. Clearly, experts in the field at and even after the priority date did not share the Examiner's belief that it was "obvious" to use a budesonide-containing medicament such as Carling's formoterol/budesonide combination in the treatment of COPD.

In sum, Applicants have established that one of ordinary skill in the art at the filing date would not have expected a budesonide-containing medicament such as Carling's formoterol/ budesonide combination to be useful for treating Smeenk's Patient B (or any other COPD patient), and so would not have thought it worth even trying. In fact, Smeenk *taught away* from using the formoterol/budesonide combination for treating his COPD patients. Smeenk disclosed that ICS (budesonide) treatment was apparently not helping the patients and was likely to have been responsible for the opportunistic lung infections each suffered while being treated with the ICS. This *teaching-away* by Smeenk is echoed by other art discussed above, and is not

countered by any evidence provided by the Examiner. Further, Applicants have established that the combination of formoterol and budesonide produces surprisingly beneficial, synergistic results that could not have been predicted in view of the art, and have provided objective evidence proving that at least some experts in the field of COPD remained skeptical even after the present application's priority date. In view of all of the above evidence and arguments, Applicants respectfully request withdrawal of the obviousness rejection and allowance of the claims.

If any issues remain, the Examiner is invited to telephone the undersigned to discuss them. The fee in the amount of $2,028.00 for excess claims is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 06275-0150003.

Respectfully submitted,

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